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(54) Title: FAMCICLOVIR MONOHYDRATE

(57) Abstract

Famciclovir monohydrate and its pharmaceutical use.

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FAMCICLOVIR MONOHYDRATE

This invention relates to a novel form of a pharmaceutical , and having pharmacological activity, to a process for its preparation and to its use as a pharmaceutical.

EP-A-182024 (Beecham Group p.l.c.), Example 2 describes a method of the preparation of famciclovir, a compound which is useful as the oral form of the compound, penciclovir which has antiviral activity against infections caused by herpesviruses, such as herpes simplex type 1, herpes simplex type 2 and varicella zoster virus, and also against Hepatitis B virus. Penciclovir and its antiviral activity is disclosed in Abstract P.V11-5 p.193 of 'Abstracts of 14th Int. Congress of Microbiology', Manchester, England 7-13 September 1986 (Boyd et. al.).

The form of famciclovir used for formulating into tablets or capsules is the anhydrous form as this form is stable and has good handling qualities for commercial production. In the case of a suspension formulation, however this form of famciclovir has potential disadvantages in terms of crystal growth in solution.

A pure, crystalline hydrate of famciclovir has been discovered, this hydrate having surprisingly improved properties, useful in a suspension formulation.

Accordingly, the present invention provides famciclovir monohydrate.

The hydrate is preferably in pharmaceutically acceptable form. By pharmaceutically acceptable form is meant, *inter alia*, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%. One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition.

The invention also provides a process for the preparation of a famciclovir monohydrate which process comprises dissolving anhydrous

famciclovir in an aqueous medium and allowing the monohydrate to precipitate out from the solution.

The anhydrous famciclovir is preferably dissolved in hot water at a temperature greater than 25 degrees centigrade, usually 50 to 60 degrees centigrade, and the hot solution allowed to cool slowly to 5 degrees centigrade with continuous stirring. The monohydrate crystals are then filtered off and allowed to dry at ambient temperature.

The monohydrate may also be formed by exposing the anhydrous form of famciclovir to an atmosphere containing a high concentration of water vapour.

The invention also provides a pharmaceutical composition comprising famciclovir monohydrate, and a pharmaceutically acceptable carrier. In particular, the invention comprises a pharmaceutical composition in the form of an aqueous suspension for oral administration.

Suspension formulations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; bulking agents such as microcystalline cellulose or silicon dioxide; flow agents such as colloidal silica; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The oral compositions may be prepared by conventional methods.

The invention further provides a method of treatment or prophylaxis of viral infections in mammals, such as humans, which comprises the administration of famciclovir monohydrate.

The amount of famciclovir in the oral dosage form will depend on the viral infection being treated, the type of patient and the frequency of administration. Unit dosages are likely to be 125, 250, 500, 750 mg or 1g, 1 to 3 times a day.

The invention also provides famciclovir monohydrate for use as an active therapeutic substance, in particular for use in the treatment of viral infections.

The following example illustrates the preparation of famciclovir monohydrate and the following comparison test results illustrate the beneficial use of famciclovir monohydrate in a suspension formation. European Journal of Pharmaceutical Sciences, Vol 4 Suppl., September 1996, S170, abstract P3.029, describes the use of FT-Raman Spectroscopy to characterise the pseudopolymorphic transformation of the anhydrate to the monohydrate, and AAPS 11th Annual Meeting, Seattle, WA, October 27-31, 1996, Abstract /.PDD 7140, *Pharm. Res.*, 13, S-267, 1996, describes the compaction induced solid state reactivity of the anhydrate.

Example

Famciclovir (150g) was dissolved in hot water (approximately 200ml at 50 to 60 degrees centigrade). The hot solution was allowed to cool slowly to 5 degrees centigrade with continuous stirring for 3 hours. The monohydrate crystals were filtered and then dried by allowing the excess water to evaporate under ambient conditions for approximately 2 days.

The monohydrate of famciclovir was characterised by infra-red spectroscopy, thermal analysis and X-ray diffraction methods. Identification was confirmed by proton nuclear magnetic resonance spectroscopy.

Water was determined at 5.3% (theoretical - 5.31%) by coulometric titration. This was confirmed by thermogravimetric analysis of the monohydrate which gave a 5.2% weight loss.

Comparison Test Results

An investigation was carried out on monohydrate crystal growth in famciclovir suspension. Two suspensions were prepared using the formulae below and were reconstituted with water.

Famciclovir Monohydrate Suspension		Famciclovir Anhydrate Suspension	
	% Composition		% Composition
Famciclovir Monohydrate	35.20	Famciclovir Anhydrate granules	34.36
Hydroxy Propyl Methyl Cellulose	3.33	Hydroxy Propyl Methyl Cellulose	3.33
Xanthan Gum	3.33	Xanthan Gum	3.33
Saccharin	1.78	Saccharin	1.78
Aspartame	2.67	Aspartame	2.67
Colloidal Silica	1.67	Colloidal Silica	1.67
Flavours	6.93	Flavours	6.93
Disodium hydrogen Phosphate dihydrate	19.56	Disodium hydrogen Phosphate dihydrate	15.6
Citric acid monohydrate	2.7	Citric acid monohydrate	2.47
Silicon Dioxide	22.38	Silicon Dioxide	27.41

The reconstituted suspension was stored at 25°C and the crystal growth monitored over a period of one week using microscopy.

The results from visual and photographic examination indicate little or no crystal growth in the monohydrate suspension whilst the crystals in the anhydrate suspension had grown to ten times their original size, making them less pharmaceutically acceptable.

Claims

1. Famciclovir monohydrate.

2. Famciclovir monohydrate in pharmaceutically acceptable form.

3. A process for the preparation of a famciclovir monohydrate which process comprises dissolving anhydrous famciclovir in an aqueous medium and allowing the monohydrate to precipitate out from the solution.

4. A process for the preparation of a famciclovir monohydrate which process comprises exposing the anhydrous form of famciclovir to an atmosphere containing a high concentration of water vapour.

5. A pharmaceutical composition comprising famciclovir monohydrate, and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition according to claim 5, in the form of an aqueous suspension for oral administration.

7. A method of treatment or prophylaxis of viral infections in mammals, such as humans, which comprises the administration of famciclovir monohydrate.

8. Famciclovir monohydrate for use as an active therapeutic substance.

9. Famciclovir monohydrate for use in the treatment of viral infections.

10. The use of famciclovir monohydrate in the manufacture of a medicament for use in the treatment of viral infections.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 97/00523

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 182 024 A (BEECHAM GROUP PLC) 28 May 1986 cited in the application see page 18; example 2 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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1

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 1997	28. 04. 97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/00523

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 7
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inc ational Application No
PCT/EP 97/00523

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 182024 A	28-05-86	AT 389118 B	25-10-89
		AU 589371 B	12-10-89
		AU 4756085 A	27-03-86
		CA 1262899 A	14-11-89
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